

CASE OF THE WEEK

PROFESSOR YASSER METWALLY

CLINICAL PICTURE:

A 57 years old male patient with a purely motor clinical manifestations in the form of left lower limb pyramidal manifestations of three months duration. The clinical picture has an insidious onset and a rapidly progressive course. (To inspect the patient's full radiological study, click on the attachment icon (The paper clip icon in the left pane) of the Acrobat reader then double click on the attached file) ([Click here](#) to download the attached file)

RADIOLOGICAL FINDINGS

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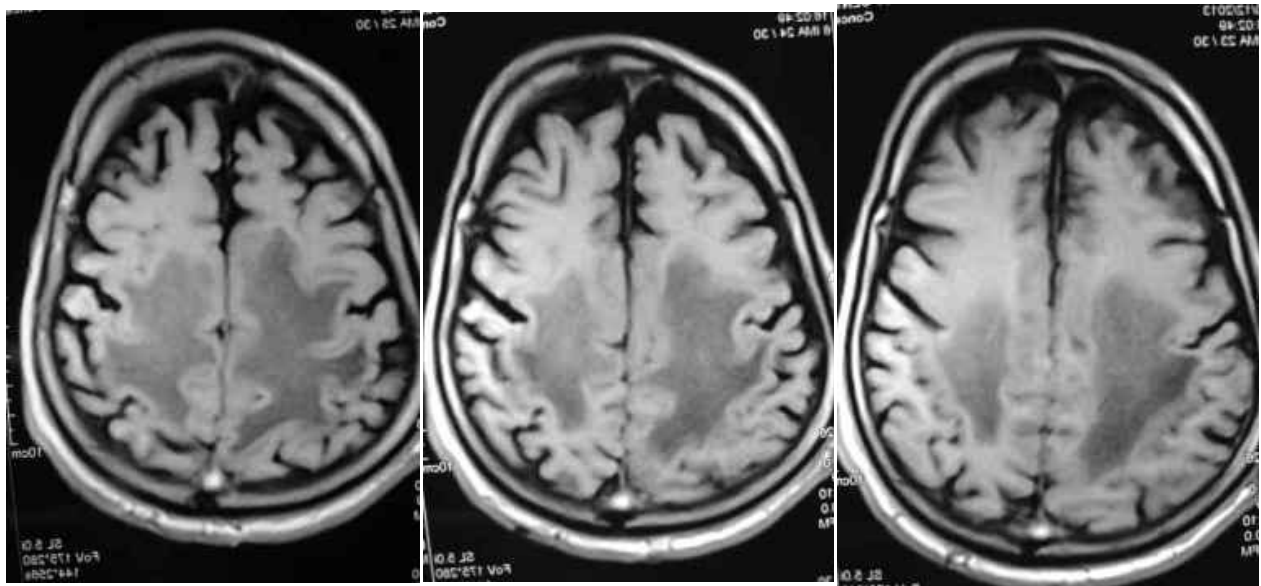


Figure 1. Precontrast T1 images (A,B) and postcontrast (C) showing bilateral, more or less symmetrical, posterior parieto-occipital white matter hypointensities with lateral scalloped margins. The T1 hypointensities is coalescent and periventricular/ subcortical in location. The scalloped lateral margin of the posterior parieto-occipital white matter T1 signal changes reflects the strictly subcortical nature of the lesion that apparently did not involve the cortical grey matter. Notice absence of contrast enhancement.

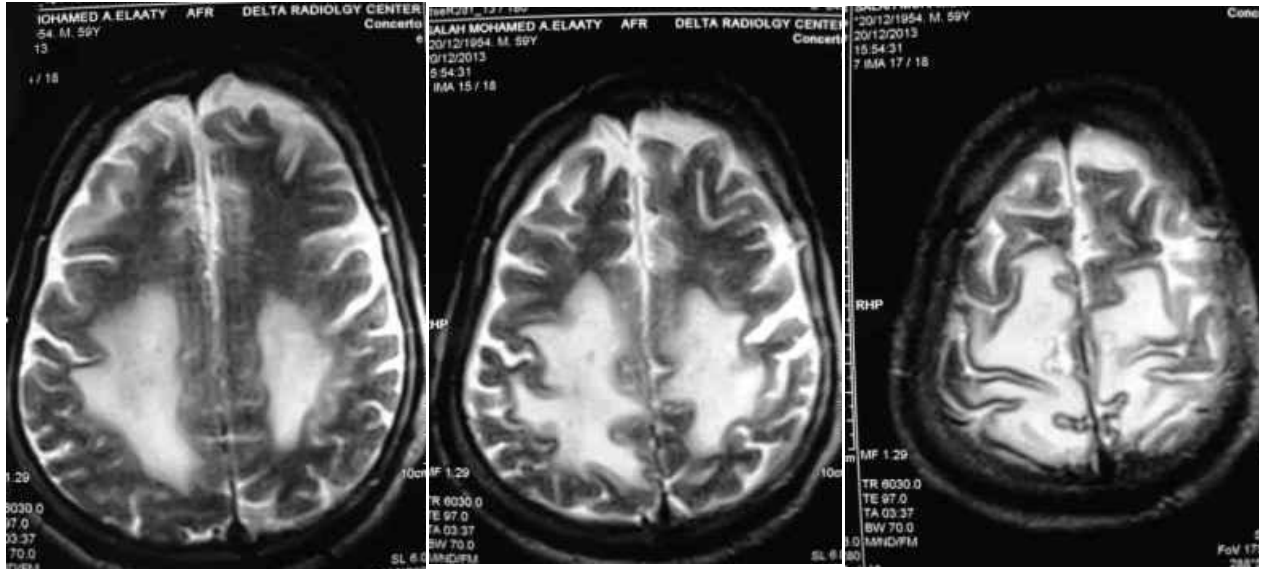


Figure 2. MRI T2 images showing bilateral, more or less symmetrical, posterior parieto-occipital white matter hyperintensity with lateral scalloped margins. The T2 hyperintensity is coalescent and periventricular/ subcortical in location. The scalloped lateral margin of the posterior parieto-occipital white matter T2 signal changes reflects the strictly subcortical nature of the lesion that apparently did not involve the cortical grey matter. The coalescent posterior parieto-occipital white matter T2 signal changes is surrounded by a continuous hypointense rim that, most probably, reflects the inflammatory nature of the lesion. The mechanism of the T2 hypointensity is not certain. Proposals in this respect include relative lack of water in the periphery of inflammatory lesion, the presence of blood products in the periphery of the lesion (Deoxyhaemoglobin/hemosiderin induce T2 hypointensity) or the presence of paramagnetic free radicals within the phagocytosing macrophages which are heterogeneously distributed in the periphery of inflammatory lesions. (Paramagnetic free radicals induce T2 hypointensity).

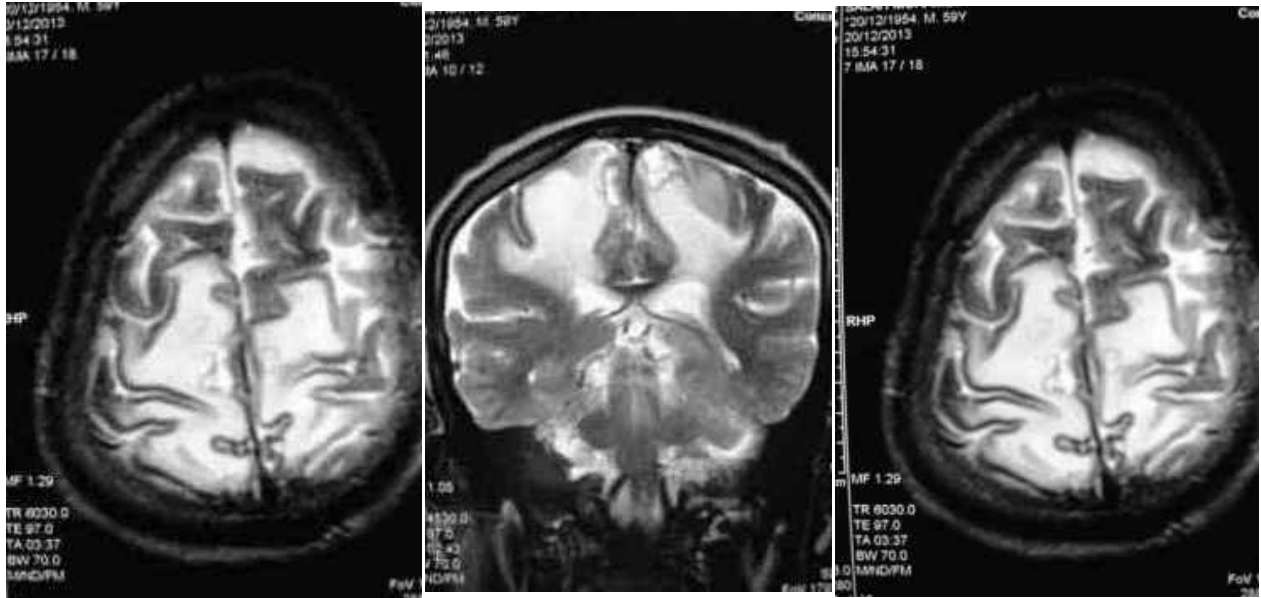


Figure 3. MRI T2 images showing bilateral, more or less symmetrical, posterior parieto-occipital white matter hyperintensity with lateral scalloped margins. The T2 hyperintensity is coalescent and periventricular/ subcortical in location. The scalloped lateral margin of the posterior parieto-occipital white matter T2 signal changes reflects the strictly subcortical nature of the lesion that apparently did not involve the cortical grey matter. The coalescent posterior parieto-occipital white matter T2 signal changes is surrounded by a continuous hypointense rim that, most probably, reflects the inflammatory nature of the lesion. The mechanism of the T2 hypointensity is not certain. Proposals in this respect include relative lack of water in the periphery of inflammatory lesion, the presence of blood products in the periphery of the lesion (Deoxyhaemoglobin/hemosiderin induce T2 hypointensity) or the presence of paramagnetic free radicals within the phagocytosing macrophages which are heterogeneously distributed in the periphery of inflammatory lesions. (Paramagnetic free radicals induce T2 hypointensity). Notice the presence popcorn-like lesions in (B) that probably reflect the existence of some vascular/venous anomalies. The findings of vascular blush and arteriovenous shunting on angiography, in progressive multifocal leukoencephalopathy, are nonspecific and was reported before. (14) Notice absence of mass effect.

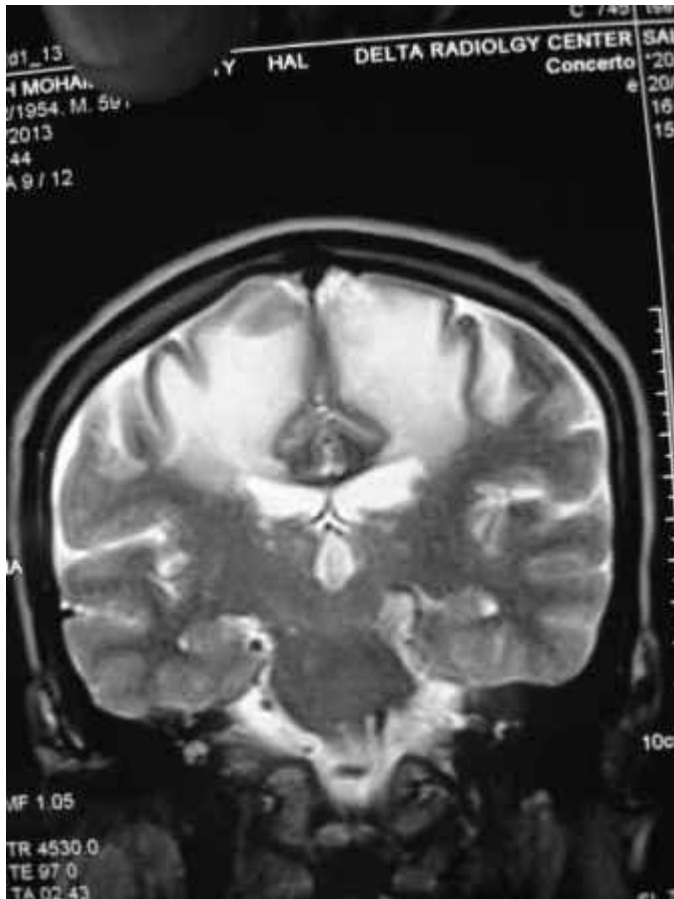


Figure 4. The coalescent posterior parieto-occipital white matter T2 signal changes is surrounded by a continuous hypointense rim that, most, probably, reflects the inflammatory nature of the lesion. The mechanism of the T2 hypointensity is not certain. Proposals in this respect include relative lack of water in the periphery of inflammatory lesion, the presence of blood products in the periphery of the lesion (deoxyhaemoglobin/hemosiderin induce T2 hypointensity) or the presence of paramagnetic free radicals within the phagocytosing macrophages which are heterogeneously distributed in the periphery of inflammatory lesions. (Paramagnetic free radicals induce T2 hypointensity). Multiple foci of acute hemorrhage and abundant petechial hemorrhages in and at the periphery of the posterior parieto-occipital white matter lesions was occasionally reported in progressive multifocal leukoencephalopathy. (14) Notice the popcorn-like lesions in this image, that probably reflect the existence of some vascular/venous anomalies. The findings of vascular blush and arteriovenous shunting on angiography, in progressive multifocal leukoencephalopathy, are nonspecific and was reported before. (14) Notice absence of mass effect.

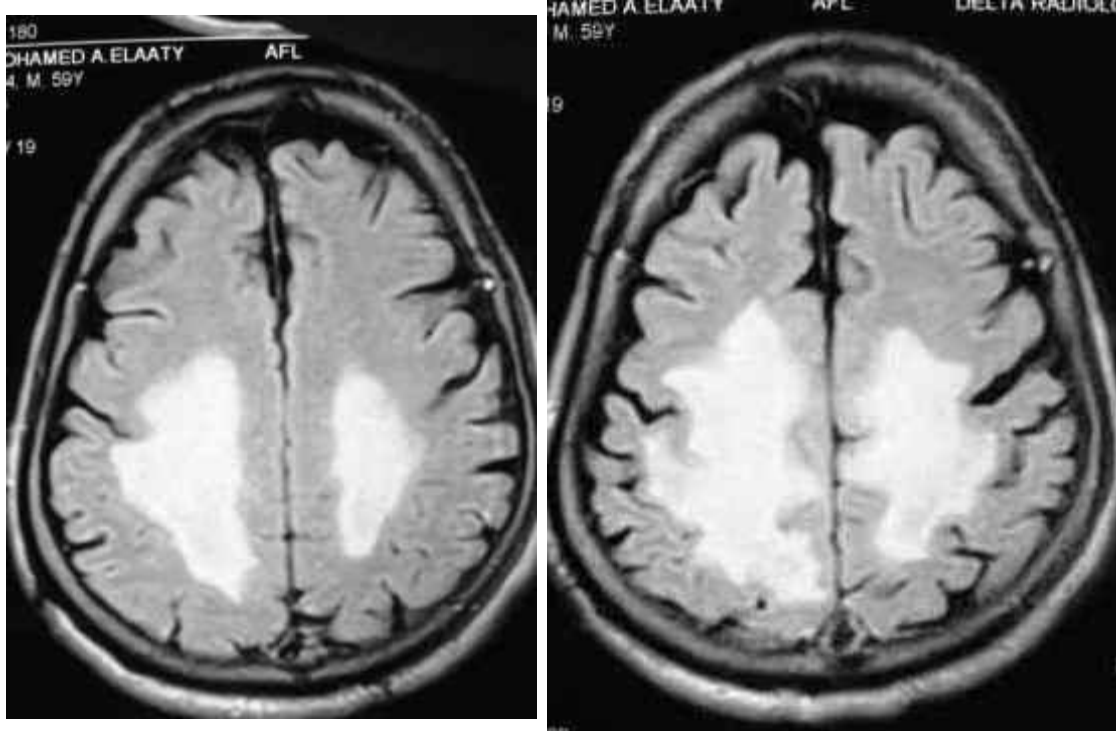


Figure 5. FLAIR MRI images showing the bilateral, more or less symmetrical, posterior parieto-occipital white matter hyperintensity with lateral scalloped margins.



Figure 6. Chest Plain X ray showing an upper quadrant lung lesion. The lesion was not biopsied in this patient.

Progressive multifocal leukoencephalopathy (PML) is a subacute opportunistic infection caused by the unenveloped DNA virus JC Polyomavirus (JCV). By the age of 65 years, 50% to 70% of individuals have antibodies to the virus. (26) After entering, the virus persists in the renal tubular epithelial cells. With reactivation of latent JCV in the kidneys and subsequent viremia, the JCV enters the brain and causes Progressive multifocal leukoencephalopathy. (26)

The incidence of progressive multifocal leukoencephalopathy has greatly increased as a result of the AIDS epidemic, and 0.7% to 11% of patients who have HIV develop progressive multifocal leukoencephalopathy during the course of their illness. The histopathologic hallmark of progressive multifocal leukoencephalopathy is demyelination with enlarged oligodendroglial nuclei and bizarre astrocytes. The disease is usually multifocal, and the lesions may occur in any location in the white matter, most often in the parieto-occipital region. Thalamic lesions are frequently present, and the cerebellum and brain stem can also be involved. Posterior fossa lesions are usually present simultaneously with supratentorial lesions, and, in rare cases, progressive multifocal leukoencephalopathy may be limited to the posterior fossa. Although there are no significant pathologic differences between patients who have and do not have AIDS, in the AIDS population, more extensive disease with a necrotizing character was observed. (26)

The findings on MR imaging correlate well with macroscopic changes. On T2-weighted MR imaging, progressive multifocal leukoencephalopathy lesions are patchy, scalloped, high signal intensity lesions located in the white matter, with extension along the white fibers. Subcortical arcuate fibers are involved, mass effect is mild or absent, and peripheral faint enhancement is a rare feature. On T1-weighted images, the progressive multifocal leukoencephalopathy lesions have low signal, in contrast to isointense HIV-associated lesions. (26)

The coalescent posterior parieto-occipital white matter T2 signal changes is sometimes surrounded by a continuous hypointense rim that, most, probably, reflects the inflammatory nature of the lesion. The mechanism of the T2 hypointensity is not certain. Proposals in this respect include relative lack of water in the periphery of inflammatory lesion, the presence of blood products in the periphery of the lesion (deoxyhaemoglobin/hemosiderin induce T2 hypointensity) or the presence of paramagnetic free radicals within the phagocytosing macrophages which are heterogeneously distributed in the periphery of inflammatory lesions. (Paramagnetic free radicals induce T2 hypointensity). Multiple foci of acute hemorrhage and abundant petechial hemorrhages in and at the periphery of the posterior parieto-occipital white matter lesions was occasionally reported in progressive multifocal leukoencephalopathy. (14) A popcorn-like lesions are sometimes reported in PML, and probably reflect the existence of some vascular/venous anomalies in PML. The findings of vascular blush and arteriovenous shunting on angiography, in progressive multifocal leukoencephalopathy, are nonspecific and was reported before. (14)

DIAGNOSIS:

DIAGNOSIS: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

DISCUSSION

DISCUSSION:

Progressive multifocal leukoencephalopathy (PML) is a fatal subacute progressive demyelinating disease seen in persons with impaired cell-mediated immune response. Progressive multifocal leukoencephalopathy predominantly occurs in patients with AIDS. Before the AIDS epidemic, Progressive multifocal leukoencephalopathy was rare and associated with immunocompromised conditions, such as leukemia, lymphoma, systemic lupus erythematosus (SLE), organ transplantation, Wiskott-Aldrich syndrome, and severe combined immunodeficiency (SCID).

At present, Progressive multifocal leukoencephalopathy develops in as many as 5% of all patients with AIDS. This demyelinating disease results from infection with the JC virus, which belongs to the genus *Polyomavirus* of the *Papovaviridae* family of viruses.

Anstrom et al first described Progressive multifocal leukoencephalopathy in 1958, and Zurhein and Chou initially demonstrated the association of Progressive multifocal

leukoencephalopathy with a viral infection. In 1971, Padgett et al confirmed the viral etiology by isolating a virus from the brain of a patient who had died from Progressive multifocal leukoencephalopathy. The patient's initials were J.C.; hence, the virus is known as the JC virus.

Progressive multifocal leukoencephalopathy is characterized by 3 cardinal histopathologic features: demyelination, enlarged nuclei of oligodendrocytes, and bizarre astrocytes.

The JC virus is believed to produce infection after it enters the tonsillar tissue during an upper respiratory tract infection. After infection, the virus becomes latent in the spleen, the reticuloendothelial system, and the medulla of the kidney. The JC virus is thought to be undetectable in the brain tissue.

Antibodies (immunoglobulin G [IgG]) to the JC virus are common in most Western populations. Seroconversion is seen in 10% of the children by the age of 5 years, in 40-60% by 10 years, and in up to 90% of young adults. Acute infection is usually not noticed. After several years of latency, reactivation occurs under appropriate conditions of immunocompromise.

Approximately 50-80% of all Progressive multifocal leukoencephalopathy cases occur in patients with HIV infection, whereas cases are rare in patients with organ transplantation. This difference may indicate the need for an interaction between the JC virus and HIV for Progressive multifocal leukoencephalopathy to develop rather than just an underlying setting of decreased immune function. Although reactivation of JC virus may be necessary, this itself is insufficient to cause Progressive multifocal leukoencephalopathy. A specific deficiency in cellular immune response to the JC viral antigen is probably required in addition to the general cellular immunodeficiency in persons with Progressive multifocal leukoencephalopathy.

Reactivation of the virus occurs in the kidney and bone marrow, usually in the setting of immunosuppression. Infected lymphocytes (B cells) then cross the blood-brain barrier and pass infection to astrocytes at the border of vessels. The infection may then be augmented by multiplication and eventual infection of adjacent oligodendrocytes. Oligodendrocytes are responsible for forming and maintaining the myelin sheath. Infection of the oligodendrocytes causes destruction of the cells and loss of the myelin sheath. The axons are usually spared.

- **Histopathology**

On microscopy, the cardinal feature of Progressive multifocal leukoencephalopathy is demyelination, which is usually multifocal. The lesions may occur in any location in the white matter, and they range from 1 mm to several centimeters in size.

The histopathologic hallmarks of Progressive multifocal leukoencephalopathy include a triad of multifocal demyelination, hyperchromatic enlarged oligodendroglial nuclei, and enlarged bizarre astrocytes with lobulated and hyperchromatic nuclei. Electron

microscopy reveals JC virus in the oligodendroglial cells. Gross examination reveals gray or brown discoloration of the affected brain as a result of loss of myelin.

In the US: The prevalence of Progressive multifocal leukoencephalopathy in patients with HIV infection is 1-5% in clinical studies, though postmortem data show a rate of up to 8%. The prevalence of this disease initially increased with the rising incidence of HIV infection, but more recently, the incidence has decreased with the widespread use of highly active antiretroviral therapy (HAART), which has reversed immunosuppression in many patients with AIDS (see subsection on Prognostic utility of MRI in Progressive multifocal leukoencephalopathy). For unknown reasons, Progressive multifocal leukoencephalopathy rarely affects children with HIV infection.

The median survival of patients with Progressive multifocal leukoencephalopathy as a complication of AIDS is 6 months. In 10% of patients, survival exceeds 12 months. The longest reported survival is 92 months from the onset of illness. Progressive multifocal leukoencephalopathy is an AIDS-defining illness. Patients whose MRIs show enhancement, which is rare, and those with an increased CD4 count appear to have a better prognosis than that of other patients; these findings probably represent their relatively good immune status. Before the AIDS epidemic, men and women were affected in a male-to female ratio of 3:2, and lymphoproliferative disease was the most common cause. At present, HIV infection is most common cause, with a male-to-female ratio of 7:1 Progressive multifocal leukoencephalopathy chiefly affects homosexual or bisexual men aged 25-50 years. For unknown reasons, Progressive multifocal leukoencephalopathy rarely affects children with HIV infection. The white matter of the brain is usually involved. Lesions of Progressive multifocal leukoencephalopathy may occur anywhere in brain, but the frontal lobes and parieto-occipital regions are commonly affected. Isolated involvement of basal ganglia, external capsule, and posterior-fossa structures may be seen.

As of now, radiographically guided intervention has no role in the treatment of Progressive multifocal leukoencephalopathy. An antiretroviral regimen containing protease inhibitors has been successful in prolonging the survival of patients with HIV infection and Progressive multifocal leukoencephalopathy. Topotecan and cidofovir are promising drugs presently under evaluation. The role of splenectomy remains unproven, though reports have described remission in association with HAART.

- **Clinical Details**
 - **Symptoms**

Progressive focal neurologic deficit is the clinical hallmark. Weakness and disturbance of speech are most common symptoms. Other symptoms include cognitive abnormalities, headaches, gait disorders, visual impairment, and sensory loss.

Headaches are most common in the HIV-infected population, and visual disturbances are most common in those without HIV infection. About 10% of patients have seizures. Cognitive deficits do not persist in isolation for long and distinguish Progressive multifocal leukoencephalopathy from HIV dementia. Progressive multifocal leukoencephalopathy

seems to have a more aggressive course in persons with HIV disease than in persons with other predisposing conditions.

- **Signs**

Most common physical sign is limb weakness, which occurs in more than 50% of patients. Cognitive disturbances and gait disorders affect 25-33%, and diplopia affects 9%. Optic-nerve disease does not occur with Progressive multifocal leukoencephalopathy, and spinal-cord involvement is rare.

- **Laboratory findings**

Severe cellular immunosuppression, as defined by a CD4 lymphocyte count of 200 cells/~L, is observed in most patients. The mean CD4 count is 84-104 cells/~L.

Results of CSF examination are usually normal or show slightly elevated protein levels. CSF study is not helpful in diagnosis except that it may help in excluding other diagnoses. Cell counts are usually less than 20 cells/~L.

Several studies demonstrated that polymerase chain reaction (PCR) study of the CSF has high sensitivity and specificity for JC virus in Progressive multifocal leukoencephalopathy, with some investigators reporting 95% sensitivity and 100% specificity.

An additional test of the CSF involves measurement of an antibody to the major structural protein of the JC virus known as VPI. The criterion standard for the diagnosis remains histologic confirmation by means of tissue biopsy. However, with a characteristic clinical and MRI pattern and a positive PCR result for JC virus in the CSF, brain biopsy is often avoided.

NEUROIMAGING

Radiographic imaging strongly supports the diagnosis of Progressive multifocal leukoencephalopathy in the appropriate clinical context. MRI is sensitive to white matter lesions and shows hyperintense lesions on T2-weighted (T2W) images in affected regions. Therefore, MRI is the preferred form of imaging. MRI is the preferred diagnostic test. Because of its superior contrast resolution, it can be used to detect subtle white matter abnormalities, whereas CT depicts the lesions at an advanced stage. Lesions are found at the gray matter–white matter interface and tend to involve the subcortical white matter. This predilection accounts for the scalloped margins of the lesions. Lesions are initially multiple and discrete, but they eventually may coalesce into large lesions. The lesions may occur anywhere, but are most often seen in the parieto-occipital and frontal lobes.

CT is often the first neuroimaging technique used, but is not as sensitive as MRI in the detection of white-matter lesions. MRI offers superior sensitivity in the detection of white-matter lesions of Progressive multifocal leukoencephalopathy, but it is contraindicated in

patients with a cardiac pacemaker, in those with MRI-incompatible implants, and those with intraocular metallic foreign bodies.

- **CT scan**

CT scans usually show several bilateral, asymmetric hypoattenuating foci of various sizes without mass effect or enhancement. The lesions may involve the periventricular white matter, subcortical white matter, or both. Subcortical U-fiber involvement results in lesions having a lateral scalloped margin that follows the gray matter–white matter junction.

Although lesions may be seen on CT scanning, MRI offers superior sensitivity in the detection and characterization of the lesions. The diagnosis may be suspected with CT, but MRI is needed for a more confident exclusion of other differential considerations. Artifacts; chronic, ischemic white-matter changes; and chronic infarcts may mimic true white-matter lesions of Progressive multifocal leukoencephalopathy.

- **MRI**

- **Findings on T1- and T2-weighted and fluid-attenuated inversion recovery images**

MRI has far greater sensitivity than other studies in detecting the lesions of Progressive multifocal leukoencephalopathy and in defining their extent of involvement. On T2W images, lesions appear hyperintense and typically involve the periventricular and subcortical white matter, having a characteristic scalloped lateral margin when they involve the subcortical white matter. Lesions are more conspicuously visualized on fluid-attenuated inversion recovery (FLAIR) images, appearing hyperintense against a background of suppressed CSF signal intensity.

Lesions appear hypointense and well demarcated on T1-weighted (T1W) images, though they may be isointense in the initial phase of the disease. Although the disease may involve any part of the brain, lesions typically occur in the parieto-occipital lobes. Lesions appear to start in the subcortical white matter before extending to the periventricular white matter. Mass effect is infrequently described and usually minimal and correlated with shorter survival when seen on initial studies.

- **Distribution of lesions**

A multifocal distribution pattern is seen. This pattern may be unilateral, but more often, it is bilateral and asymmetric. Lesions may start small, but they eventually enlarge and coalesce. Posterior-fossa involvement is common and is seen in up to one third of patients. Synchronous lesions are usually seen in the supratentorial compartment, though in 10% of patients, lesions are confined to the structures of the posterior fossa. Progressive multifocal leukoencephalopathy may also appear to involve the basal ganglia and deep gray-matter nuclei because of white-matter fibers in these structures. When present, involvement of the gray matter is a secondary finding. In rare cases, lesions are single and can occur anywhere in the brain, including the brainstem.

- **Findings on contrast-enhanced images**

The lesions typically do not enhance and do not have mass effect; however, some reports describe lesions with faint peripheral enhancement or diffuse enhancement with mass effect, especially in the early stages. Enhancement could suggest a relatively good immune response and hence an improved prognosis.

- **Findings on diffusion-weighted images**

On diffusion-weighted images (DWI), lesions can show restricted diffusion, though this is uncommon. The extent of abnormal diffusion appears to be correlated with the speed of clinical progression. Areas with DWI abnormality may correspond to areas that are actively infected by the virus at the time of imaging, but this has been uncommonly reported.

- **Prognostic utility of MRI in Progressive multifocal leukoencephalopathy**

Post et al (1999) studied the prognostic utility of MRI in Progressive multifocal leukoencephalopathy. None of the MRI variables was predictive of patient survival, with the exception of mass effect, which was usually minimal, infrequent, and associated with decreased survival. Serial MRI studies showed progression of disease in 1-24 weeks, and a more rapid change was seen in many patients in just 9 weeks.

The authors suggested that findings of increasing atrophy, increasing confluence and extent of white-matter lesions, spread of disease across the corpus callosum, and increasing hypointensity of the lesions on follow-up T1W MRIs may be poor prognostic indicators or as failure of response to therapy. Stabilization or a decrease in the size of the lesion, clinical improvement, and loss JC viral detection on CSF PCR testing may indicate a response to therapy. However, improvements on MRI can lag clinical improvement by 2-6 months or even indicate temporary worsening.

In Progressive multifocal leukoencephalopathy patients undergoing HAART, MRIs can show initial worsening in the first few months followed by stabilization and regression by 12 months. HAART consists of a combination of 3 or 4 anti-HIV drugs from the following classes: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.

Thurnher et al (2001) reported 2 patients with long-term responses to HAART, apparent increased mass effect and enhancement before eventual improvement, and atrophy of the involved brain parenchyma. T1W MRIs but not FLAIR MRIs showed hypointensity. Two nonresponders initially had extensive changes, without enhancement or mass effect after the start of therapy. Their T1W MRIs also showed hypointense areas that were hyperintense on FLAIR images.

This increasing hypointensity on T1W MRIs might have been due to increasing demyelination, which appears hyperintense on FLAIR images. This finding might indicate

a worsened prognosis. Increased T1W hypointensity in responders was due to gliosis and necrosis seen in burned-out lesions; this finding is hypointense on FLAIR images.

Berger et al (*Ann Neurol*, 1998) found enhancement in 8.9% of short-term survivors in contrast to 50% in long-term survivors. Enhancement suggests an improved immune response and hence an improved prognosis.

In a study by Collazos et al (1999), contrast enhancement was seen on images in patients with Progressive multifocal leukoencephalopathy treated with HAART only when their CD4⁺ count increased. In these patients, the Progressive multifocal leukoencephalopathy lesions changed from enhancing to nonenhancing on follow-up MRI after 3-6 months of therapy. Larger studies than this are needed to clearly identify the MRI changes after therapy and to confirm the utility of MRI in assessing the patient's prognosis and response to therapy.

- **Magnetic resonance spectroscopy**

Evaluation of the Progressive multifocal leukoencephalopathy lesions with magnetic resonance (MR) spectroscopy reveals reduced *N*-acetylaspartate (NAA) and creatine levels, increased choline levels, and an excess of lipids and sometimes of myo-inositol. In some cases, lactate is present. Cell membrane and myelin breakdown is the presumed cause of elevated choline levels, neuronal loss leads to decreased NAA concentrations, and glial-cells proliferation elevates myo-inositol values. The mild elevation of lactate and lipid levels may be due to the activity of macrophages and the breakdown products of myelin.

The elevation of choline and myo-inositol values is seen in the early phase of the disease. In the later phase all the metabolites are decreased. These metabolic abnormalities are not specific for Progressive multifocal leukoencephalopathy and may be similar in other lesions complicating HIV disease.

- **Magnetization transfer imaging**

Progressive multifocal leukoencephalopathy lesions appear to have strongly reduced magnetization transfer ratios. According to Ernst et al (1999), these features may help in distinguishing lesions from white-matter lesions of HIV leukoencephalopathy. Large prospective studies are needed to assess the utility of newer MR techniques, such as MR spectroscopy and magnetization transfer imaging, in the diagnosis and follow-up of Progressive multifocal leukoencephalopathy.

Degree of Confidence: MRI has far greater sensitivity than that of other studies in depicting the lesions of Progressive multifocal leukoencephalopathy and in defining their extent of involvement. Although MRI results may suggest the diagnosis of Progressive multifocal leukoencephalopathy in the appropriate clinical setting, typical features of Progressive multifocal leukoencephalopathy are often nonspecific, and other differential considerations, such as ischemic changes, HIV leukoencephalopathy, and gliotic changes from previous trauma, must be considered. When the lesions of Progressive multifocal

leukoencephalopathy are atypically enhancing or when they have mass effect, other lesions, such as those due to toxoplasmosis, lymphoma, or other intracranial masses should be considered.

The presence of multiple pathologies in immunocompromised conditions adds to the complexity of image interpretation. Infection coexisting with other opportunistic infection may be responsible for some atypical manifestations of the disease and for an apparent response to some form of therapy in some patients.

It is unusual for a normal variant to mimic Progressive multifocal leukoencephalopathy lesions on MRI. Progressive multifocal leukoencephalopathy must be distinguished from HIV leukoencephalopathy. Progressive multifocal leukoencephalopathy tends to be multifocal, with bilateral, asymmetric, and predominantly subcortical involvement. In comparison, HIV leukoencephalopathy tends to produce lesions that are usually diffuse, bilateral, and symmetric; these predominantly affect the periventricular white matter.

Diffuse cortical atrophy and ventricular dilatation are not predominant findings of Progressive multifocal leukoencephalopathy and may be helpful in distinguishing from HIV leukoencephalopathy, which is usually associated with substantial atrophy. Lesions appear well defined and hypointense on T1W images, whereas they appear isointense and poorly defined in HIV leukoencephalopathy. Clinical correlation may be helpful, as patients with Progressive multifocal leukoencephalopathy have progressive focal motor and sensory neurologic deficits, whereas those with HIV leukoencephalopathy present with global cognitive changes and dementia.

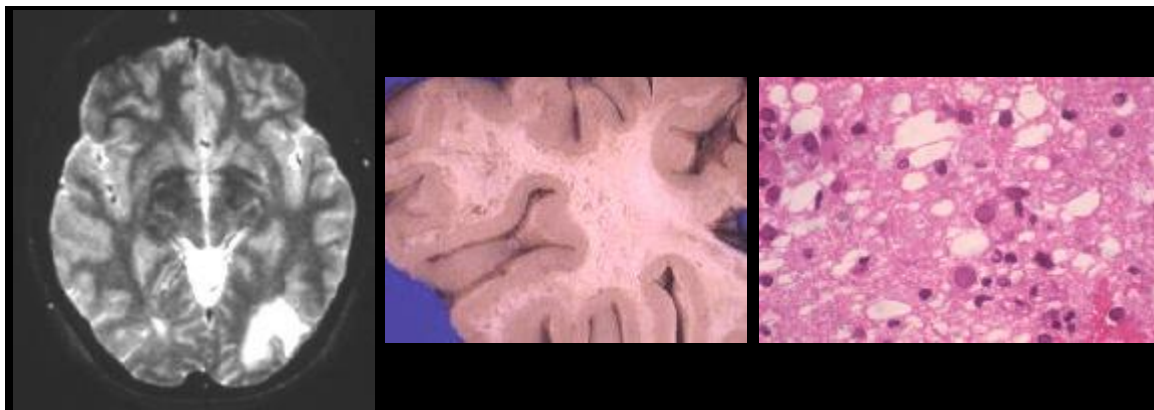


Figure 7. T2-weighted MRI shows left occipital hyperintense white matter changes with the lesion margin reaching the cortex., This sliced fixed brain shows multiple isolated or confluent gray demyelinated foci. Atrophy may be present., Microscopically, multiple demyelinated foci are detected. The microscopic hallmark of the disease is intranuclear basophilic or eosinophilic inclusions within the swollen nuclei of oligodendrocytes, often at the periphery of lesions. Large, occasionally multinucleated astrocytes with prominent processes are another characteristic feature.

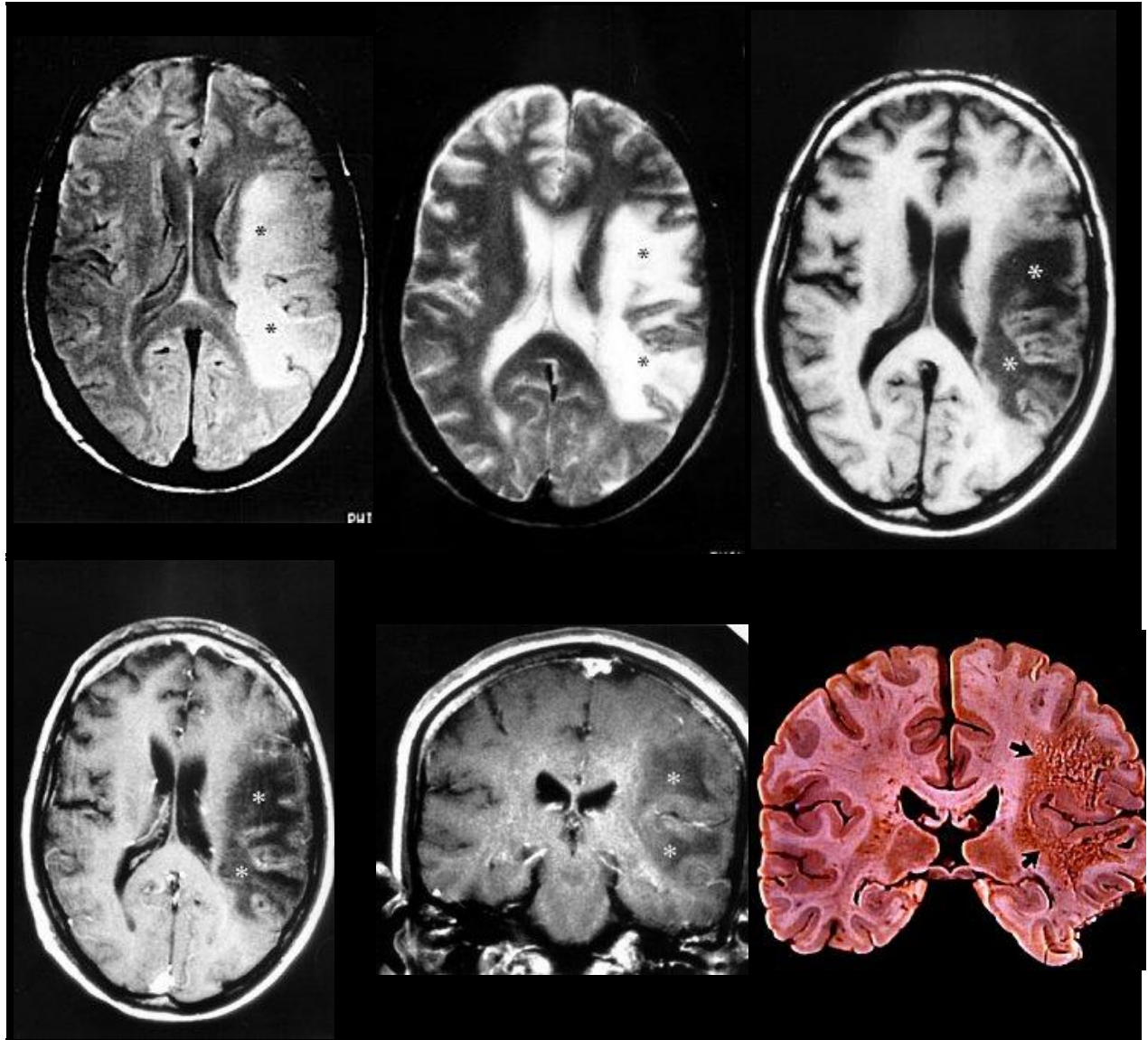


Figure 8. Progressive multifocal leukoencephalopathy, A, Axial PD (A) and T2W (B) images show large confluent area of hyperintensity (*) of left frontotemporal region. While there is some sulcal and ventricular effacement secondary to edema, the amount of edema and mass effect present is disproportionately small, given the large area of hyperintensity. Pre-contrast axial T1W (C) image shows corresponding. B, Axial PD (A) and T2W (B) images show large confluent area of hyperintensity (*) of left frontotemporal region. While there is some sulcal and ventricular effacement secondary to edema, the amount of edema and mass effect present is disproportionately small, given the large area of hyperintensity. Pre-contrast axial T1W (C) image shows corresponding region of hypointensity . C, Axial PD (A) and T2W (B) images show large confluent area of hyperintensity (*) of left frontotemporal region. While there is some sulcal and ventricular effacement secondary to edema, the amount of edema and mass effect present is disproportionately small, given the large area of hyperintensity. Pre-contrast axial T1W (C) image shows corresponding region of hypointensity . D, Post-contrast axial (D) and coronal (E) T1W images show minimal

enhancement along lateral margins of mass (*). The cortical surface is spared. E, Post-contrast axial (D) and coronal (E) T1W images show minimal enhancement along lateral margins of mass (*). The cortical surface is spared. F, Coronal autopsy specimen shows large area (arrows) of demyelination of left frontal and temporal lobes with sparing of the cortical surface.

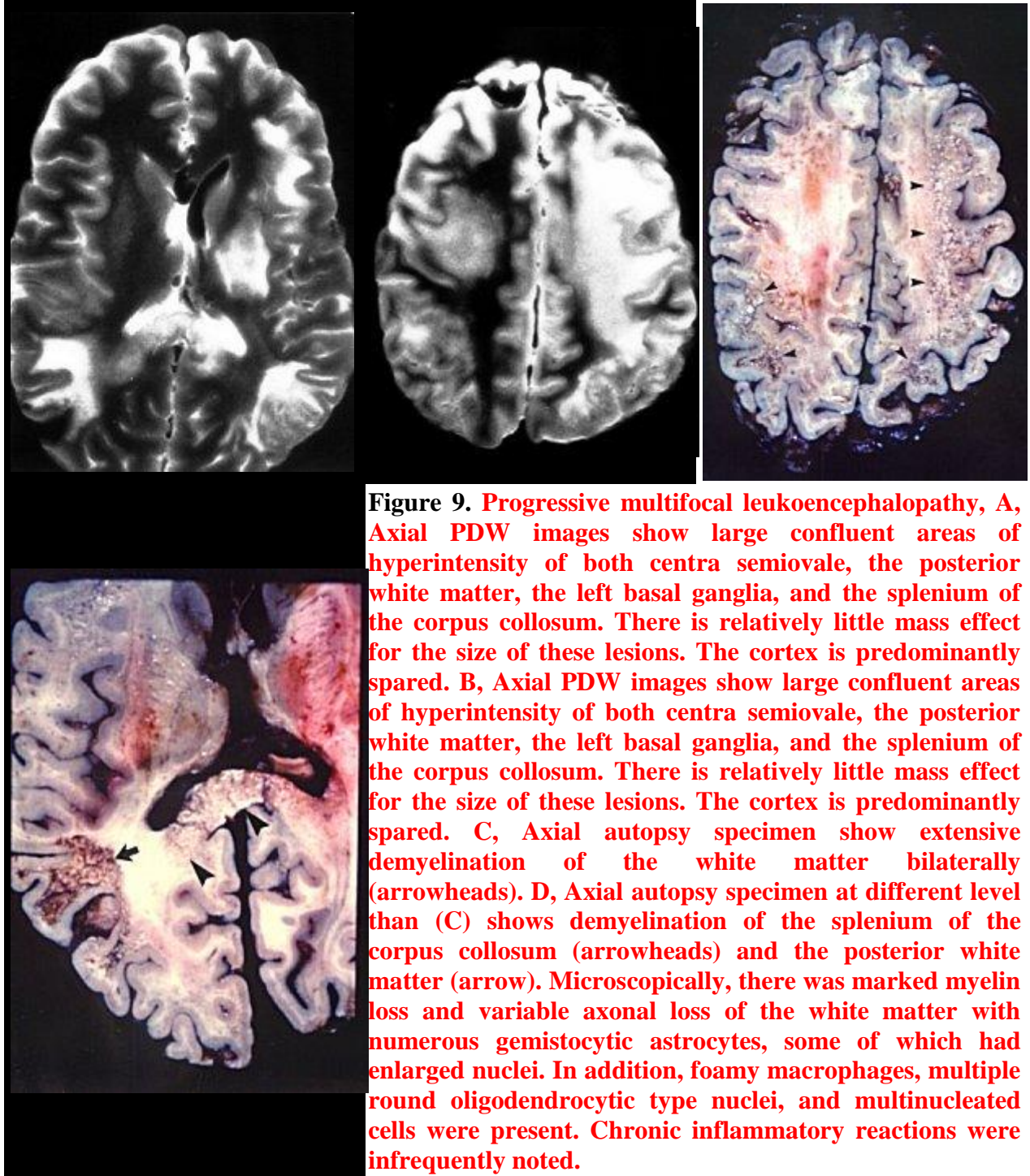


Figure 9. Progressive multifocal leukoencephalopathy, A, Axial PDW images show large confluent areas of hyperintensity of both centra semiovale, the posterior white matter, the left basal ganglia, and the splenium of the corpus collosum. There is relatively little mass effect for the size of these lesions. The cortex is predominantly spared. B, Axial PDW images show large confluent areas of hyperintensity of both centra semiovale, the posterior white matter, the left basal ganglia, and the splenium of the corpus collosum. There is relatively little mass effect for the size of these lesions. The cortex is predominantly spared. C, Axial autopsy specimen show extensive demyelination of the white matter bilaterally (arrowheads). D, Axial autopsy specimen at different level than (C) shows demyelination of the splenium of the corpus collosum (arrowheads) and the posterior white matter (arrow). Microscopically, there was marked myelin loss and variable axonal loss of the white matter with numerous gemistocytic astrocytes, some of which had enlarged nuclei. In addition, foamy macrophages, multiple round oligodendrocytic type nuclei, and multinucleated cells were present. Chronic inflammatory reactions were infrequently noted.

- **Nuclear medicine**

Nuclear medicine studies do not play a major role in the diagnosis of Progressive multifocal leukoencephalopathy. However, Port et al (1999) described a case of Progressive multifocal leukoencephalopathy in a patient with AIDS in whom MRIs of the lesion showed enhancement and mass effect, with increased thallium-201 uptake on single photon emission CT (SPECT). O'Mally et al (1994) had reported a case of Progressive multifocal leukoencephalopathy with no uptake on ²⁰¹Th SPECT.

On thallium SPECT, photopenic lesions can be caused by any previous insult to the brain parenchyma, and hence, the differential considerations include a wide variety of causes. The uncommon observation of increased radiotracer uptake may be seen with lymphoma and is atypically found in some infections. No anatomic variants have been described to mimic the lesions of Progressive multifocal leukoencephalopathy, but cold lesions (eg, arachnoid cyst, porencephalic cyst) can conceivably appear as photopenic lesions similar to the lesions of Progressive multifocal leukoencephalopathy.

- **Angiography**

Angiography has no role in the diagnosis of Progressive multifocal leukoencephalopathy. However, Nelson et al (1999) reported angiographic findings in 6 patients with Progressive multifocal leukoencephalopathy. In 4, angiograms showed abnormal parenchymal blush of the affected region in the early to mid arterial phase and persisting into the venous phase. Associated arteriovenous shunting was also present. In only 1 of the 4 patients did MRI demonstrate enhancement.

On pathologic evaluation, intense perivascular inflammatory cellular infiltrates, angiogenesis, and gliosis were found in the patients with angiographic abnormalities, whereas changes were minimal in patients who did not have angiographic abnormalities. The findings of vascular blush and arteriovenous shunting on angiography are nonspecific and can be seen with infectious, neoplastic, vascular, and ischemic etiologies.

SUMMARY

SUMMARY

Progressive multifocal leukoencephalopathy is an uncommon progressive fatal demyelinating disease that affects immunocompromised patients. The cause is a papovavirus—the Creutzfeldt-Jakob virus. The lesions are usually multifocal and asymmetric, most commonly affecting the subcortical white matter and corpus callosum. In the corpus callosum, focal lesions can occur that enlarge and become confluent as the disease progresses. The lesions are hyperintense on long-TR sequences and hypointense on

short-TR/TE sequences. The lesions usually do not enhance, although they may enhance faintly at the periphery. Progressive multifocal leukoencephalopathy should be considered in the differential diagnosis of space-occupying lesions in HIV patients. The lack of enhancement and mass effect can act as features differentiating this entity from others such as lymphoma or glioblastoma.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by an infection of papovavirus and for many years was known as a rare complication in immunocompromised patients with lymphoma, sarcoidosis, or following transplant surgery.

Progressive multifocal leukoencephalopathy has become a relatively common complication of acquired immunodeficiency syndrome (AIDS) patients. 10,21 Apparently, Progressive multifocal leukoencephalopathy lesions in AIDS patients are more destructive, and show a higher density of papovavirus-infected cells. On CT, the Progressive multifocal leukoencephalopathy lesions are multifocal, initially involving subcortical white matter, progressing to involve deeper white matter, and typically are of low density without significant enhancement, mass effect, or edema. The MR imaging diagnosis of Progressive multifocal leukoencephalopathy is facilitated by knowledge of the patient's immunocompromised state. Geographic or maplike regions of increased water content are seen on MR images as decreased signal on T1-weighted images, and increased signal on proton density and T2-weighted images. Peripheral enhancement and hemorrhage are rare but have been described.

The brain may appear completely normal on external examination. On sectioning, however, typical multifocal demyelinating lesions of Progressive multifocal leukoencephalopathy usually are found in the subcortical white matter. In long-lasting cases, large confluent areas of demyelination may extend into deep white matter, accompanied by many small satellite foci. In the well-fixed brain, smaller foci of demyelination usually are discolored gray, whereas the surface of larger lesions may be granular, with a moth-eaten appearance. Extensively involved white matter may be discolored yellow, necrotic, or cavitated. The cerebrum is commonly involved; however, lesions in the cerebellum and brainstem, with or without cerebral involvement, have been reported. The histology of the lesions varies considerably depending on the stage of the disease process. In very early stages, the changes may be subtle, and scattered reactive astrocytes without any obvious foci of demyelination may be the only changes seen in the white matter. Within typical small foci of demyelination are many reactive astrocytes, some showing bizarre nuclei suggestive of neoplastic astrocytes. Reactive microglia/macrophages also are present. Oligodendrocytes usually are found in the peripheral zone of these foci of demyelination. Their nuclei often are enlarged, glassy, and homogeneously amphophilic to mildly basophilic. The nuclei of these oligodendrocytes are immunostained with the antibody to the papovavirus and harbor virions, as detected with the electron microscope. Viral antigen also can be detected in the nuclei with in situ hybridization. In large confluent lesions, it is common to find packed reactive astrocytes and foamy, lipid-containing macrophages occupying most of the lesion.

- **Addendum**

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